UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/978,192 | 10/15/2001 | Avi J. Ashkenazi | GNE.2630P1C9 | 3437 |

7590 08/19/2008

GINGER R DREGER
HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025

| EXAMINER | |
|---|---|
| SAOUD, CHRISTINE J | |
| ART UNIT | PAPER NUMBER |
| 1647 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/19/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/978,192 | ASHKENAZI ET AL. | |
| | Examiner | Art Unit | |
| | Christine J. Saoud | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *58-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Applicant, Amendments, And/Or Claims*

The Appeal Brief filed 11 April 2008 has been received and considered. Upon further consideration, finality of the previous Office Action (mailed 01 November 2006) is withdrawn solely to clarify the issues for appeal, and to provide Applicant with an opportunity to respond accordingly.

Claims 58-62 are pending in the instant application. Claims 1-57 have been canceled in a previous amendment.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 11 April 2008 have been fully considered but they are not deemed to be persuasive.

### *35 U.S.C. §§ 101 and 112, First Paragraph*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-62 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility, for the reasons of record in the previous Office actions

Claims 58-62 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth in the instant Office action and for the reasons previously made of record, one skilled in the art clearly would not know how to use the claimed invention.

A portion of the basis for these rejections is withdrawn. Specifically, the Examiner no longer asserts that **mRNA levels** are not predictive of polypeptide levels. Therefore, the following references are no longer being relied upon to support the rejections: Gygi et al., Hu et al., Nagaraja et al, Waghray et al. and Sagynaliev et al. The following references cited by Applicant pertaining to the mRNA/polypeptide correlation issue will no longer be addressed: Futcher et al., Alberts and Lewin, and Meric et al. The basis for the maintained rejections is solely that **gene amplification levels** are not predictive of mRNA or polypeptide levels.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to isolated antibodies which binds to the polypeptide of SEQ ID NO: 7, wherein the antibody is monoclonal, humanized, a fragment or labeled.

The specification discloses the polypeptide of SEQ ID NO: 7, also known as PRO274. Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides.

At pages 331-345 of the specification, Example 114 discloses a gene amplification assay in which genomic DNA encoding PRO274 had a ΔCt value of at least 1.0 for three out of nineteen lung tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 114 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer. ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 341-345 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

First, there are several problems with the data provided in this example. Only three out of the nineteen lung cancer samples tested positive. Therefore, if a sample were taken from an individual with lung cancer for diagnosis, ***it is more likely than not that this assay would yield a false negative result***. Furthermore, the art recognizes

that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO274 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO274 is a diagnostic probe for lung cancer or that antibodies which bind PRO274 could be used to detect lung cancer unless it is clear that PRO274 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, and even if a majority of tumor samples had tested positive, the data have no bearing on the utility of the claimed PRO274 antibodies. In order for PRO274 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO274 mRNA or PRO274 polypeptide levels in lung tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by

Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

The *general* concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Hittelman also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) speak to general

lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "***It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO274 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic

DNA including the gene being studied gene is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO274.

Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) speak to general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a***

***selective advantage to the cells in which they are amplified***." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "***It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO274 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic DNA including the gene being studied gene is amplified.

Therefore, data pertaining to PRO274 genomic DNA do not indicate anything significant regarding the claimed antibodies which bind PRO274 polypeptides. The data do not support the specification's assertion that PRO274 antibodies can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO274 polypeptides are overexpressed in

any cancer to the extent that the antibodies which bind them could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO274 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO274 polypeptides as diagnostic markers and the claimed antibodies to detect them are simply starting points for further research and investigation into potential practical uses of the claimed antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., and Li et al.) the rejections are properly maintained.

***Response to Arguments***

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons.

Beginning at page 10 of the response, Applicant reviews Example 114 and the data in Table 9, and asserts that an amplification of at least 2-fold is significant and

indicative of a cancer diagnostic marker. However, the issue is whether or not a 2.0-3.05 fold amplification of the gene encoding PRO274 in three out of 19 lung tumor samples is significant. In the instant case, the facts are that sixteen of the nineteen lung tumor samples did not show an amplification of the gene encoding PRO274, and the control used was not a matched non-tumor lung sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Hittelman, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, this argument does not speak to whether or not the encoded proteins are also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

Beginning at page 11 of the response, Applicant refers to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 14 September 2004 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the previous Office actions for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's

opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2 to 3.05-fold amplification of the gene encoding PRO274 in three lung tumors is significant. The significance can be questioned based on the absence of factual support for the expert's opinion. In the instant case, the facts are that sixteen of the nineteen lung tumor samples did not show an amplification of the gene encoding PRO274, and the control used was not a matched non-tumor lung sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Hittelman, Godbout et al., and Li et al. references, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins are also found at increased levels in cancerous tissues.

Applicant argues at pages 11-12 of the response that the articles of Orntoft. et al., Hyman et al. and Pollack et al. teach that in general, gene amplification increases mRNA expression. Applicant further argues that over a hundred references, along with Declarations have been submitted that in general, there is a correlation between mRNA levels and polypeptide levels.

This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Applicant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner asserts that 2% does not provide a reasonable expectation that the slight amplification of PRO274 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer.

Applicant also refers to the declarations of Dr. Polakis, submitted under 37 C.F.R. § 1.132 on 14 September 2004 and 03 August 2006. Applicant previously characterized the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were

found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicant previously concluded that all of the submitted evidence supports Applicant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO274 (i.e., data regarding amplification of PRO274 genomic DNA), and does not disclose any information regarding PRO274 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels.

See, e.g., Pennica et al., Konopka et al., Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), Haynes et al., Lian et al., and Fessler et al. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

Applicant argues at page 13 of the response that they have shown significant DNA amplification in three lung tumor samples in Table 9, Example 114 and the fact that not all lung tumors tested positive in this study does not make the gene amplification data less significant. Applicant also states that rare tumor markers have great value in tumor diagnosis. Applicant's argument has been fully considered, but is not persuasive. As stated previously, the data presented in Example 114 is based on genomic DNA and one cannot extrapolate from genomic DNA to protein levels, therefore, the instant specification does not indicate that PRO274 protein is elevated in lung tumors such that it would be considered a diagnostic marker for lung cancer, absent evidence to the contrary. Applicant cites Hanna and Mornin (submitted 14 September 2004) as support for the assertion that some tumor markers are useful for identifying rare malignancies. A review of Hanna and Mornin (1999, Pathology Associates Medical Laboratories) provides another important example of a lack of correlation between gene amplification and mRNA/protein overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu

gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin evidenced that the level of protein expression must be tested empirically to determine whether or not the protein can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the protein level of PRO274 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

Applicant asserts at page 14 of the response that even if there were no correlation between gene amplification and mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer still has a patentable utility in that it yields more accurate tumor classification and provides significant information for cancer diagnosis and treatment, relying upon the declaration by Dr. Ashkenzi (submitted 14 September 2004). Finally, Applicant concludes that there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO274 conveys utility to the claimed PRO274 antibodies. These arguments have been fully considered but are not found to be persuasive. While it may be true that lack of overexpression of a gene product may also provide useful information in tumor categorization, the specification does not disclose such further testing of PRO274 gene product expression levels to facilitate categorization. Therefore, the skilled artisan would have been required to do the

testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form. Furthermore, the specification provides no assertion that the claimed PRO274 antibodies are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO274. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial. Finally, Hanna et al. supports the rejection in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. Hanna et al. say these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "In general, FISH [gene] and IHC[protein] results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." This teaches away from using gene amplification in cancer diagnosis or treatment. The identification of subsets of tumors without correlation affirms the unpredictability of the findings. Therefore, the issues of HER-2 cannot be generalized to any gene expressed in a tumor. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments to reasonably confirm the real world context of the asserted

utility. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Again, because Hanna et al. studied breast cancer, the warning by Pollack et al. relating to the disparity in correlation of gene amplification and expression in breast compared to colon tumors is significant.

Applicant asserts at page 15 of the response that a *prima facie* case of lack of utility has not been established. Applicant asserts that it is not legally required that there be a necessary correlation between the data presented and the claimed subject matter. Applicant further argues that the evidentiary standard is a preponderance of the totality of the evidence under consideration. Applicant concludes that the question is whether it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation between gene copy number and protein expression levels.

Applicant's arguments have been fully considered, but are not persuasive. Applicant's assessment of the question to be asked is on point and correct. However, a review of the totality of the evidence under consideration must result in the conclusion that one skilled in the art would reasonably doubt the existence of a positive correlation between protein expression and gene copy number.

Applicant argues at page 16 that Pennica et al. showed a correlation between DNA amplification and overexpression for WISP-1 and that a change in mRNA without a change in DNA copy number is not contrary to Applicant's assertions. Applicant argues that the fact that the single WISP-2 gene did not show the expected correlation of gene amplification with the level of mRNA/protein expression does not establish that it is

more likely than not, in general, that such correlation does not exist. Applicant asserts that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, as was demonstrated for WISP-1.

Applicant's argument has been fully considered, but is not persuasive. Alleging that the working hypothesis among those skilled in the art without supporting evidence is an assertion, not a fact. The evidence of record demonstrates that there is not a predictable correlation between DNA amplification and overexpression - Pennica et al. is a reference which clearly demonstrates the difficulties and lack of correlation especially in cancer tissues. Therefore, data pertaining to PRO274 nucleic acids do not necessarily indicate anything significant regarding the claimed PRO274 antibodies and the data do not support the assertion that PRO274 can be used as a cancer diagnostic.

Applicant argues at page 17 of the response that Pennica et al. is specific to WISP genes and that Pennica et al. teaches nothing whatsoever about the correlation of gene amplification and protein expression in general. This has been fully considered, but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica and Konopka constitute evidence that it cannot be assumed that amplified genomic DNA results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect. Finally, Sen, and Hittelman constitute evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer.

At pages 17-19, Applicant addresses Gygi et al. However, the teachings of Gygi et al. do not relate to the issue in the instant application which is the ability, or lack thereof, to predict protein expression levels from genomic DNA levels. Gygi et al. is directed to mRNA, and therefore, is not on point with the issues of the instant application.

At pages 19-21, Applicant addresses Hu et al. However, the teachings of Hu et al. do not relate to the issue in the instant application which is the ability, or lack thereof, to predict protein expression levels from genomic DNA levels. Hu et al. is directed to mRNA and micro array, therefore, it is not on point with the issues of the instant application.

At page 21 of the response, Applicant addresses Li et al. Applicant argues that Li et al. acknowledge their results differed from those of Hyman et al. and Pollack et al., who found a substantially higher level of correlation between gene amplification and increased gene expression", with Li et al. noting the difference may be from different methods used to study breast cancer and lung adenocarcinoma. Li et al. used a lower fold amplification threshold (1.40 compared to 2.0 in the instant application). The argument has been fully considered, but is not persuasive. Even if Li et al. used a lower amplification threshold, it was shown that a *significant majority* of genes that are amplified do not have overexpressed mRNA (p. 2633, col. 2, end of first paragraph):

> In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but lack biological relevance in terms of the development of lung adenocarcinoma.

Similarly, Hyman et al. found less than half (44%) of *highly* amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Like Hyman et al., Pollack et al. concentrated on large chromosome regions showing *high* amplification (p. 12965). Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability for any particular gene. PRO274 gene has not been asserted to be amplified in breast tumors. Both Li et al. and Hyman et al. show that less than half of the genes showing amplified DNA also showed elevated expression of mRNA. These references in combination with other references such as Godbout et al., Pennica et al. and Konopka et al. support a conclusion that one of skill in the art would not reasonably expect that for any particular amplified gene the corresponding mRNA or protein will more likely than not also be overexpressed.

At pages 22-25, Applicant addresses Nagaraja et al., Waghray et al. and Sagynaliiev et al. However, as pointed out previously, these references are not directed to the issue of the instant application, which is the lack of correlation of genomic DNA levels on protein expression levels. Therefore, comments regarding these references are not material to the rejections of record.

Applicant argues at page 26 of the response that ample evidence has been provided to show that, in general, if a gene is amplified in cancer, it is more likely than not that the corresponding mRNA and encoded polypeptide are also expressed at an

elevated level. Applicant refers to Orntoft et al., Hyman et al. and Pollack et al. as teaching that, in general, gene amplification increases mRNA expression. Additionally, it is argued that Hyman et al. and Pollack et al. did not use traditional CGH analysis to identify amplified genes, while they did analyzed copy number on a gene-by-gene basis. These arguments have been fully considered but are not found to be persuasive. Orntoft et al. looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region (see for example, p 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with clusters of chromosomal material containing strong gains, but it is not known whether PRO274 is in a gene cluster in a region of a chromosome that is highly amplified, which is pertinent because Orntoft et al. only provide information about genes in clusters (large chromosomal regions). The data of Orntoft et al. are not from looking at a 1:1 correspondence of genomic DNA and the mRNA which is transcribed from it. If PRO274 is not part of a cluster showing strong gains, then the findings of Orntoft et al. are not applicable. Because no such information was disclosed for PRO274, Orntoft et al. does not support Applicant's position. Ornoft et al. go on to say that detection was very limited.

While Hyman et al. and Pollack et al. combined CGH with microarray analysis,

the results do not support a conclusion that the skilled artisan would reasonably expect amplified genomic DNA to correspond with overexpression of encoded protein. Hyman et al. used CGH in combination with cDNA microarray analysis. Less than half (44%) of *highly* amplified genes showed mRNA overexpression, and 10.5% of highly overexpressed transcripts had amplified genes (p. 6242, col. 1, third full paragraph). Thus, even at the level of high amplification and high overexpression, the two do not usually correlate. Polypeptide levels were not investigated. Further, Hyman et al. state that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributed to gene amplification (col. 1, middle, p. 6244). This proportion was about 2% of the total. The Examiner maintains that 2% does not provide a reasonably expectation that the amplification of PRO274 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, the references supports the basis of the rejections that it is more likely than not that gene amplification fails to correlate with increased mRNA/polypeptide levels. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. concentrated on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, Platzer et al., who found a poor correlation between DNA amplification and overexpression (p. 12967, col. 2, 7 lines from bottom). Pollack et al. noted that, “Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this

issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability, particularly when gene amplification of the instant PRO274 gene has been identified in lung cancer instead of breast tumors.

Applicant also refers to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed August 3, 2006. This declaration was addressed earlier, in that the instant specification only discloses gene amplification data for PRO274 and does not disclose any information regarding PRO274 mRNA levels.and that there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues. Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them.

At page 28 of the response, Applicant refers to the sale of gene expression chips to measure mRNA levels. However, this information is not relevant to the claimed invention because the claimed invention is not directed to gene expression chips, but rather an antibody that binds the protein of SEQ ID NO:7. Sales of the chips do not indicate anything regarding what the research community believes concerning information to be gained from the chips related to protein levels, contrary to Applicant's assertion. One cannot determine the motives or beliefs of the public based on the purchase of a company's product.

At page 29 of the response, Applicant asserts that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Applicant continues to address the Polakis declaration at pages 29-

31, however, the Examiner already conceded this point (mRNA and protein levels) and this is not the issue in the instant application, but rather that genomic DNA is not predictive of protein expression levels.

At page 32 of the response, Applicant addresses the Meric et al. reference. However, as stated previously, Meric et al. relates to mRNA levels and protein expression, which is not the issue in the instant application. Therefore, arguments related to this reference are not relevant and need not be addressed.

Applicant argues at page 35 of the response that the claimed antibodies would have diagnositic utility even if there is no direct correlation between gene expression and encoded polypeptide. Applicant refers to the Ashkenazi Declaration submitted 14 September 2004, that "even when amplification of a cancer marker gene does not result in significant over-expresison in the corresonding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment". The Declaration has been fully considered, but the arguments are not persuasive. First, the utility of the encoded polypeptides (and therefore, the antibodies which bind them) on their face has been addressed above. As stated previously, the data and evidence in the specification is too sparce for one of ordinary skill in the art to make any reasonable conclusions as to the utility of the encoded polypeptides and their antibodies for diagnostic purposes because only the genomic DNA was measured, because of aneuploidy, because no information is provided on expression levels of the protein, because there is no information on what type of lung tumor tissues were tested, etc. Applicant refers to the declaration of Dr. Ashkenazi as indicating that simultaneous

testing of gene expression and gene product enables more accurate tumor classification, even if there is no positive correlation between the two. The Declaration of Dr. Ashkenazi explains that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment, in that if the gene product is over-expressed in some tumor types but not others, this would enable more accurate tumor classification and hence better determination of suitable therapy, and additionally, if a gene is amplified by the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product

The declaration filed under 37 CFR 1.132 filed 14 September 2004 is insufficient to overcome the rejection of the claims based upon lack of utility because: it has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors. If it was, the protein would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment. The argument that if a gene is amplified but the gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target the gene product is also insufficient to overcome the rejection of the claims. If a specific gene product was known to be involved in cancer and if there were known compounds that could be used to target the gene product, this would be an acceptable utility. However, the gene product of the instant invention has not been demonstrated to be involved in

cancer. Over-expression of a gene product in a cancer cell does not necessarily mean that the gene product is involved in the cancer and that targeting the gene product would be therapeutic. Additionally, there are no known compounds that would target the gene product.

Applicant provides the Hanna et al. reference to support the Declaration of Dr. Ashkenazi. The Hanna reference is not applicable to the instant fact situation, as it deals with a known tumor associated gene, and not with a prospective analysis of the type found in this specification. The Hanna reference was addressed more fully earlier in the Office action above. Applicant asserts at page 35 of the response that PRO274 is a tumor associated gene and in the majority of amplified genes, the teachings in the art overwhelmingly show that gene ampliification influences gene expression at the mRNA and protein levels and that based on the amplification data for the PRO274 gene, the polypeptide is ocncomitantly overexpressed.

Applicant's argument has been fully considered, but is not persuasive. Regarding the gene amplification assay itself, it is noted that PRO274 gene was not amplified in 16 out of 19 lung carcinoma. Therefore, PRO274 it is more likely than not that a lung carcinoma sample will not have amplified PRO274. Also, the assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged lung epithelium (evidenced by Hittelman). Contrary to Applicant's assertion, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Konopka et al., Godbout et al., Hyman et al., and Li et al. Since significant further research would have

been required of the skilled artisan to reasonably confirm that the claimed PRO274 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. Even more research would be required of the skilled artisan to determine if the claimed PRO274 polypeptides could be used as a cancer therapeutic, since there is no evidence that PRO290 plays a role in cancer formation or progression such that inhibiting PRO274 would result in effective cancer therapy. In the absence of information regarding whether or not PRO274 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO274 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicant argues at pages 36-37 of the response that the arguments directed to the utility rejection overcome the rejection of the claims for lack of enablement. Applicant's arguments have been fully considered, but are not persuasive. As the rejection under 35 USC 101 is maintained for the reasons presented above, the

rejection of the claims under 35 USC 112/1st paragraph is also maintained for those same reasons.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 58-62 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ho et al., Science, Vol. 289, July 14, 2000, pages 265-270, for reasons of record in the previous Office Actions.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 59-62 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al., Science, Vol. 289, July 14, 2000, pages 265-270, in view of Immunobiology, The Immune System in Health and Disease, Third Edition, Janeway, And Travers, Ed., 1997, for reasons of record in the previous Office Actions.

Applicant traverses the rejections and asserts that they rely on the gene amplification assay for patentable utility which was first disclosed in International

Application no. PCT/US00/03565, filed Feb. 11, 2000, and asserts that they are entitled to at least that filing date, so that Ho et al. is not prior art. Applicant's arguments have been fully considered but are not deemed persuasive, because the gene amplification assay fails to provide a patentable utility for the antibodies to the protein, for reasons discussed above.

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647